

Antidepressants in intensive care survivors: neuroimmune modulation, clinical outcomes, and translational implications

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Abstract

Neuropsychiatric sequelae following critical illness are increasingly recognized as major determinants of long-term morbidity and mortality. Depression affects approximately one-third of intensive care unit (ICU) survivors and contributes significantly to post-intensive care syndrome (PICS). Recent epidemiological data demonstrate substantial initiation of antidepressant therapy following ICU discharge, while clinical cohort studies confirm a high burden of depressive symptoms among survivors. Beyond their classical monoaminergic mechanisms, antidepressants exert profound neuroimmune regulatory effects, including suppression of pro-inflammatory cytokines, modulation of the NLRP3 inflammasome, and restoration of neuroplasticity. However, psychotropic drug use in critically ill populations carries safety challenges and complex pharmacokinetic considerations. This mini-review synthesizes epidemiological, clinical, and mechanistic evidence to examine the dual role of antidepressants in ICU survivors: as therapeutic agents for mood disorders and as modulators of neuroimmune dysregulation. The review highlights translational opportunities and identifies key areas for precision-based interventions in critical care psychiatry.

Keywords: Antidepressants, Depression, Neuroinflammation, Neuroimmune modulation, Critical illness, Psychotropic drugs, Translational psychiatry

Introduction

Advances in modern intensive care medicine have dramatically improved survival rates. However, improved survival has unveiled a substantial burden of long-term psychological and cognitive impairment among ICU survivors. Depression, anxiety, and post-traumatic stress symptoms form a core component of post-intensive care syndrome (PICS), significantly affecting quality of life and mortality risk [1,2]. A nationwide Swedish cohort study including more than 125,000 ICU survivors demonstrated that 7% initiated antidepressant therapy within three months of discharge and 15.5% within one year [1]. These findings highlight the urgent need for integrative frameworks that bridge neuroimmune biology with practical psychiatric management strategies in ICU follow-up care. Importantly, antidepressant initiation was associated with increased mortality, including deaths due to external causes and suicide [1]. These findings underscore the clinical relevance of post-ICU depression and the urgent need for mechanistic understanding and optimized therapeutic strategies. Parallel clinical observations in ICU survivor clinics reveal that nearly one-third of patients exhibit moderate-to-severe depressive symptoms during follow-up [2]. Despite this high prevalence, the biological underpinnings linking critical illness, systemic inflammation, and depressive symptomatology remain incompletely defined [3,4].

Neuroimmune Dysregulation in Depression and Critical Illness

Recent studies clearly connect depression with immune system imbalance [3,4]. Individuals with major depressive disorder (MDD) frequently have increased blood levels of IL-1 β , IL-6, TNF- α ,

and interferon- γ [3]. Neuroinflammation diminishes neurotrophic support, notably brain-derived neurotrophic factor (BDNF), which harms synaptic plasticity and neuronal resilience [3]. The inflammatory theory of depression involves more than just elevated cytokines. Activation of the NLRP3 inflammasome, a complex responsible for maturing IL-1 β and IL-18, is key in neuroimmune communication [4]. Its activation is associated with stress-related depression and synaptic problems [4]. Critical illness triggers a severe systemic inflammatory response. Cytokine storms, endothelial damage, oxidative stress, and blood-brain barrier leaks expose the brain to ongoing inflammation [1]. ICU settings worsen this by causing delirium, sleep issues, immobility, and psychological trauma [1,5]. Microglia in the brain—similar to those involved in MDD—likely play a role in post-ICU cognitive and emotional issues [3]. Persistent inflammation can alter tryptophan metabolism through indoleamine 2,3-dioxygenase (IDO), lowering serotonin levels and boosting kynurenine pathway products, which are associated with depression [3]. Understanding these converging inflammatory pathways may enable clinicians to identify biologically vulnerable ICU survivors who require early psychiatric surveillance and targeted intervention. Consequently, ICU-related depression might stem from a combination of systemic and neuroimmune inflammation, providing a biological basis for antidepressants to serve both mood-enhancing and immune-modulating functions [3,4].

Immunomodulatory Mechanisms of Antidepressants

While traditional models focus on blocking monoamine reuptake, recent research shows antidepressants also influence immune cytokine networks [3,6]. A detailed review of neuroimmune regulation indicates that antidepressants consistently lower pro-inflammatory cytokines such as IFN- γ , TNF- α , and IL-6, and boost anti-inflammatory factors like IL-10 and TGF- β [3,7]. These effects are observed across various drug classes, suggesting immune modulation is a core component of their therapeutic effect rather than merely a side effect [3,6]. The NLRP3 inflammasome is increasingly recognized as a critical target in depression; many antidepressants diminish inflammasome activation and IL-1 β signaling [4,8]. Reducing inflammasome-related neuroinflammation helps restore synaptic plasticity and enhances stress resilience [4]. Furthermore, antidepressants affect microglial polarization, shifting from a pro-inflammatory to a regulatory profile [3,9]. Because microglia play a central role in neuroinflammation associated with critical illness, this mechanism is especially relevant for ICU patients [5]. Newer antidepressants promote rapid synapse formation by modulating glutamate pathways and increasing BDNF levels [10]. For instance, ketamine derivatives enhance synaptic connections in prefrontal circuits and act quickly as antidepressants [10]. Restoring neuroplasticity may be vital for ICU survivors, who often experience cognitive impairment due to prolonged sedation, delirium, and inflammation [1]. By promoting CREB phosphorylation and BDNF production, antidepressants may help counteract the structural synaptic deficits linked to PICS [3,10].

Mechanistic specificity of antidepressant classes in critical care contexts

Apart from their general immune-modulating effects, some antidepressant classes operate through specific mechanisms that may be especially relevant for ICU patients. For example, Selective Serotonin Reuptake Inhibitors (SSRIs) boost serotonin levels at

synapses by blocking the serotonin transporter (SERT) [11]. This action activates 5-HT_{1A} receptors, which subsequently affect cyclic AMP pathways and increase BDNF gene transcription through CREB [12,13]. Furthermore, SSRIs diminish microglial activation and suppress NF- κ B signaling, leading to lower levels of IL-6 and TNF- α [14]. These actions may help alleviate depression symptoms linked to inflammation following critical illness. Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) enhance noradrenergic activity by affecting arousal systems controlled by the locus coeruleus [15], possibly aiding in the reduction of post-ICU fatigue and cognitive issues. This noradrenergic modulation also affects peripheral immune signals and blood vessel regulation, which may support neurovascular recovery following systemic inflammation [16].

Ketamine: Rapid antidepressant and neuroprotective mechanisms in ICU settings

Ketamine warrants special consideration due to its unique pharmacological characteristics and established use in critical care. Being a non-competitive NMDA receptor antagonist, it primarily blocks NMDA receptors on GABAergic interneurons, causing a temporary rise in glutamate levels and enhancing AMPA receptor activity [17]. This process triggers the mTOR signaling pathway, which accelerates synaptogenesis and dendritic spine growth in prefrontal cortical circuits [18]. Activation of mTOR and its downstream effectors boosts BDNF translation and promotes synaptic protein synthesis, thereby restoring the deficits in synapses caused by stress [19]. These quick neuroplastic changes set ketamine apart from traditional monoaminergic antidepressants, which usually take several weeks to show clinical benefits. Importantly, ketamine's anti-inflammatory effects occur independently of monoaminergic pathways. Experimental studies show it can inhibit NLRP3 inflammasome activation, lower IL-1 β release, reduce microglial activation, and diminish oxidative stress [20]. These effects could be especially beneficial for ICU survivors who experience cytokine storms and systemic inflammation. In addition to its antidepressant effects, ketamine is frequently used in neurointensive care to manage refractory status epilepticus and suppress spreading depolarizations [21,22]. By inhibiting spreading depolarizations and stabilizing cortical networks, ketamine may confer neuroprotective and mood-stabilizing benefits for severely ill patients. Due to its combined antidepressant, analgesic, anti-inflammatory, and neuroprotective effects, ketamine stands out as a uniquely mechanistic therapeutic option for post-ICU neuropsychiatric recovery.

Clinical Evidence of Antidepressant Use in ICU Survivors

A nationwide Swedish study identified several predictors for initiating antidepressant treatment after ICU discharge, including female gender, psychiatric comorbidities, substance dependence, and more severe illness [1]. Routine screening protocols within ICU recovery clinics may therefore benefit from incorporating both psychiatric history and markers of illness severity when stratifying post-discharge depression risk. Patients on antidepressants had higher mortality rates, raising questions about whether this indicates greater illness severity, poor treatment response, or broader psychosocial vulnerabilities [1]. Data from ICU survivor clinics show that many still experience depressive symptoms despite being on antidepressants [2]. Younger age and socioeconomic status were

associated with higher depression levels, underscoring the complex, multifactorial nature of mood disorders following ICU care [2]. These results imply that antidepressants alone may be insufficient without a comprehensive approach incorporating neuroimmune and psychosocial evaluations [2,3]. Administering psychotropic drugs to critically ill patients poses specific challenges. ICU patients are prone to adverse reactions and interactions, especially with drugs like benzodiazepines, which are commonly used for sedation and can increase delirium risk and impair neurocognitive outcomes [5]. Although antidepressants may sometimes be continued or initiated during hospitalization, experts advise caution against routine use during acute instability [5]. Variations in drug pharmacokinetics due to ICU-related conditions such as liver and kidney dysfunction, protein-binding changes, and polypharmacy add further complexity to dosing [5]. These pharmacokinetic complexities are particularly relevant for agents such as ketamine, whose hepatic metabolism (*via CYP2B6* and *CYP3A4*) and active metabolites (e.g., hydroxynorketamine) may exhibit variable kinetics in organ dysfunction. Careful dose titration and monitoring are therefore essential when integrating rapid-acting antidepressant strategies into ICU or post-ICU care pathways. These factors highlight the importance of tailoring pharmacological treatments to each patient.

Translational Implications and Future Directions

The convergence of large-scale epidemiological data, clinical cohort observations, and mechanistic neuroimmune research provides a compelling framework for translational innovation in post-ICU depression. Nationwide registry analyses demonstrate substantial initiation of antidepressant therapy following intensive care discharge, underscoring the magnitude of psychiatric morbidity in this population [1]. Parallel findings from ICU recovery clinics confirm persistent depressive symptoms despite pharmacological treatment, highlighting the need for more biologically informed strategies [2]. At the mechanistic level, accumulating evidence indicates that antidepressants exert significant immunomodulatory effects, including suppression of pro-inflammatory cytokines such as IL-6 and TNF- α and restoration of anti-inflammatory signalling networks [3]. These insights suggest that biomarker-guided stratification based on inflammatory profiles may help identify ICU survivors most likely to benefit from immunoregulatory antidepressant interventions. Furthermore, the central role of the NLRP3 inflammasome in neuroimmune activation supports exploration of adjunctive strategies targeting inflammasome signaling to enhance therapeutic response. Rapid-acting glutamatergic agents that promote synaptic repair and neuroplastic recovery may offer particular advantages during early post-ICU rehabilitation [5]. Finally, integration of structured psychiatric assessment and multidisciplinary follow-up within ICU recovery clinics represents an essential component of comprehensive care, ensuring that biological and psychosocial determinants of depression are addressed in tandem. Collectively, these translational pathways redefine antidepressants not merely as mood-modifying agents but as modulators of neuroimmune homeostasis within critical care recovery paradigms. Depression among ICU survivors reflects a multifactorial interplay between systemic inflammation, neuroimmune activation, and psychosocial vulnerability that emerges during and after critical illness. Large-scale epidemiological investigations demonstrate substantial initiation of antidepressant therapy following ICU discharge, yet long-term clinical outcomes remain heterogeneous, suggesting that pharmacological treatment alone does not uniformly

resolve post-ICU depressive symptomatology. Mechanistic research increasingly supports the concept that antidepressants exert meaningful immunomodulatory actions beyond monoamine reuptake inhibition, including regulation of pro- and anti-inflammatory cytokines, attenuation of inflammasome signalling pathways, and restoration of neuroplastic processes such as BDNF-mediated synaptic remodelling. These biological properties provide a plausible rationale for their therapeutic role in inflammation-associated depression that develops in the aftermath of critical illness. Nevertheless, the complex pharmacokinetic environment of the ICU characterized by organ dysfunction, polypharmacy, and vulnerability to adverse drug reactions necessitates cautious implementation and individualized risk assessment. Future investigations should integrate biomarker-driven stratification, mechanistic clinical trials, and longitudinal neurocognitive follow-up to establish precision-based strategies for managing post-ICU depression. In this context, antidepressants should be conceptualized not solely as mood-modifying agents but as modulators of neuroimmune homeostasis, a paradigm that may reshape therapeutic frameworks within critical care psychiatry and improve long-term recovery trajectories for ICU survivors.

Conflicts of Interest

The authors declare no conflicts of interest.

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Author Contributions

Durairaj Ragu Varman-Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, Fairen Angelin Jayakumar -Writing – review & editing

Abbreviations

BDNF: Brain-Derived Neurotrophic Factor; BBB: Blood–Brain Barrier; CREB: cAMP Response Element-Binding Protein; CRP: C-Reactive Protein; CYP: Cytochrome P450; HPA: Hypothalamic–Pituitary–Adrenal; ICU : Intensive Care Unit; IDO: Indoleamine 2,3-Dioxygenase; IFN- γ : Interferon Gamma; IL: Interleukin; MDD: Major Depressive Disorder; NF- κ B: Nuclear Factor Kappa B; NLRP3: NOD-Like Receptor Family Pyrin Domain Containing; PICS: Post-Intensive Care Syndrome; PTSD: Post-Traumatic Stress Disorder; ROS: Reactive Oxygen Species; SSRI : Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin–Norepinephrine Reuptake Inhibitor; TNF- α : Tumor Necrosis Factor Alpha

References

1. von Oelreich E, Eriksson J, Eriksson M, Larsson E, Oldner A. Antidepressant drug use after intensive care: a nationwide cohort study. *Sci Rep.* 2024 Jul 9;14(1):15863.
2. Wang S, Mosher C, Gao S, Kirk K, Lasiter S, Khan S, et al. Antidepressant Use and Depressive Symptoms in Intensive Care Unit Survivors. *J Hosp Med.* 2017 Sep;12(9):731–4.
3. Nava RG, Adri AS, Filgueiras IS, Nobile AL, Barcelos PM, Corrêa YLG, et al. Modulation of neuroimmune cytokine networks by antidepressants: implications in mood regulation. *Transl Psychiatry.* 2025 Aug 23;15(1):314.

4. Lv S, Kong L, Zhong X, Shang R, Lu Y, Zhang G, et al. Natural antidepressants in neuroimmunomodulation: molecular mechanisms, action targets, and therapeutic potential. *Front Immunol*. 2025 Aug 27;16:1642001.
5. Shafiekhani M, Mirjalili M, Vazin A. Psychotropic drug therapy in patients in the intensive care unit - usage, adverse effects, and drug interactions: a review. *Ther Clin Risk Manag*. 2018 Sep 28;14:1799–812.
6. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol*. 2016 Jan;16(1):22–34.
7. Köhler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatr Scand*. 2017 May;135(5):373–87.
8. Alcocer-Gómez E, Casas-Barquero N, Williams MR, Romero-Guillena SL, Cañadas-Lozano D, Bullón P, et al. Antidepressants induce autophagy dependent-NLRP3-inflammasome inhibition in Major depressive disorder. *Pharmacol Res*. 2017 Jul;121:114–21.
9. Yirmiya R, Rimmerman N, Reshef R. Depression as a microglial disease. *Trends Neurosci*. 2015 Oct;38(10):637–58.
10. Duman RS, Aghajanian GK, Sanacora G, Krystal JH. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med*. 2016 Mar;22(3):238–49.
11. Blier P, El Mansari M. Serotonin and beyond: therapeutics for major depression. *Philos Trans R Soc Lond B Biol Sci*. 2013 Feb 25;368(1615):20120536.
12. Nibuya M, Nestler EJ, Duman RS. Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. *J Neurosci*. 1996 Apr 1;16(7):2365–72.
13. Castrén E, Monteggia LM. Brain-Derived Neurotrophic Factor Signaling in Depression and Antidepressant Action. *Biol Psychiatry*. 2021 Jul 15;90(2):128–36.
14. Hannestad J, DellaGioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. *Neuropsychopharmacology*. 2011 Nov;36(12):2452–9.
15. Berridge CW, Waterhouse BD. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Res Brain Res Rev*. 2003 Apr;42(1):33–84.
16. Heesen C, Schulz KH, Fiehler J, Von der Mark U, Otte C, Jung R, et al. Correlates of cognitive dysfunction in multiple sclerosis. *Brain Behav Immun*. 2010 Oct;24(7):1148–55.
17. Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, et al. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature*. 2011 Jun 15;475(7354):91–5.
18. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*. 2010 Aug 20;329(5994):959–64.
19. Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. *Mol Psychiatry*. 2018 Apr;23(4):801–11.
20. Loix S, De Kock M, Henin P. The anti-inflammatory effects of ketamine: state of the art. *Acta Anaesthesiol Belg*. 2011;62(1):47–58.
21. Carlson AP, Abbas M, Alunday RL, Qeadan F, Shuttleworth CW. Spreading depolarization in acute brain injury inhibited by ketamine: a prospective, randomized, multiple crossover trial. *J Neurosurg*. 2018 May 25;130(5):1513–9.
22. Alkhachroum A, Der-Nigoghossian CA, Mathews E, Massad N, Letchinger R, Doyle K, et al. Ketamine to treat super-refractory status epilepticus. *Neurology*. 2020 Oct 20;95(16):e2286–94.